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Critical Periods for the Development of Obesity

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1. Introduction

The mother's nutritional and metabolic environment is critical in determining not only the success of reproduction but also for the future health of the newborn. Maternal genetics, maternal diet during pregnancy, lactation and infant feeding in the early stages of life can have long-term effects on children's health and may predispose to diseases such as obesity. The term "*programming*" has been used to describe the process by which stimuli or manipulations applied during critical or sensitive periods of development and organogenesis can cause changes in the long term in structures and functions of the body, compromising the future health of the individual (Barker, 1994; Lucas, 1994; Symonds et al., 2007). The concept "*programming*" defines the genetic, diet, nutrition and habits in the early stages of life for the pregnant mother and child, which are main factors influencing the optimal neurological and psychological development of children (Dunstan et al., 2008; Helland et al., 2003; Hibbeln et al., 2005; Wells, 2007) and the development of diseases in adulthood (Lucas, 2005; Wells, 2007) such as diabetes (Fernández-Twinn & Ozanne, 2006), obesity (Budge et al., 2005; Koletzko, 2006), cardiovascular disease (Feldt et al., 2007), some types of cancer (Key et al., 2004) and bone diseases (Sayer & Cooper, 2005) (Figure 1).

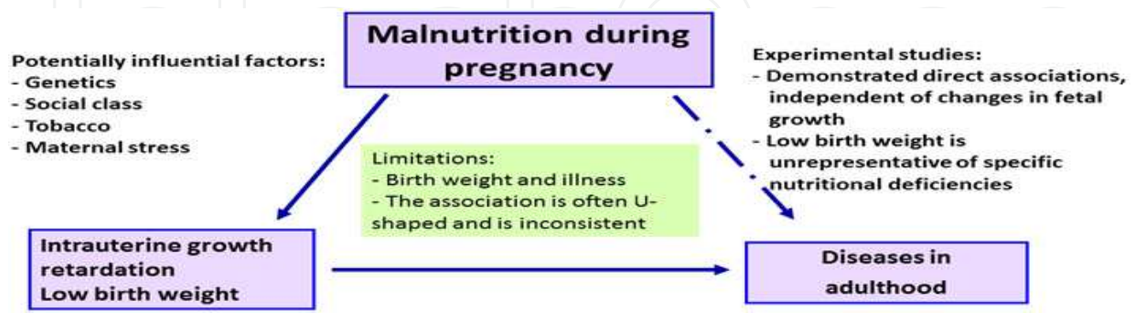

Fig. 1. The different factors that can affect the long-term health of the newborn

Studies have shown that maternal nutrition during pregnancy (Krauss-Etschmann et al., 2007; Lucas, 2005), breastfeeding (Koletzko, 2006) and complementary feeding can influence children's development and long-term health (Demmelmair et al., 2006). It has also been

demonstrated that birth weight can have a significant effect on the interaction between fat and muscle metabolism (Symonds et al., 2006).

2. Programming of obesity from early stages in life

In the early 50's, Widdowson & McCance, 1963, began to study in animal models the influence of pre- and postnatal diet on the development of obesity. These researchers found that rats born with low weight and subsequently overfed during postnatal life, developed a large size and body weight in adulthood; the rats overfed during early lactation, showed high concentrations of insulin and cholesterol. Since then, numerous studies have shown that obesity, a plague in Western countries, may have its roots before birth (Cottrell & Ozanne, 2008). However, much remains to be elucidated about how the human body records these impressions. Given that obesity is primarily a disorder of energy balance, where energy intake exceeds energy expenditure, its mechanisms may involve the regulation of appetite and a disruption of energy expenditure together with an alteration of tissue metabolism and physical activity (Taylor & Poston, 2007).

Currently there is scientific evidence from both epidemiological and animal studies suggesting that programming of obesity is caused by environmental influences that occur from the embryonic stage to neonatal life and childhood. Studies in animal models show that the foetus and newborn may be receiving different hormonal and dietary insults that converge in a common phenotype of hyperphagia, obesity, impaired adipocyte function and alteration of physical activity. Although the programming of obesity is clearly a multifactorial process, the diversity of models with a common goal allows suggesting some common metabolic pathways. The change in adipocyte development and the stimulation of the secretion of glucocorticoids seems to play an important role in the plasticity of the hypothalamus at the end of gestation and early postnatal life and is also clearly involved in programming appetite and metabolism to establish a higher body weight, which may or may not be adjusted over time (Taylor & Poston, 2007).

Different mechanisms during critical stages of development may be involved in the early programming of adult obesity, including:

1. Impairment of placental function,
2. Formation of foetal adipose tissue and regulation of leptin synthesis and secretion before birth (McMillen et al., 2006; Singhal et al., 2002),
3. Some genes related to the development of obesity: FTO, INSIG 2, MC4R, Pro12AlA and PPARγ2 Ala12Ala, LEP, POMC polymorphisms C8246T and C1032G, ... (Creemers et al., 2008; Hinney et al., 2007; Loos et al., 2008) and epigenetic alteration of the foetal genome,
4. Prenatal nutrition, birth weight and growth rate in postnatal life (McMillen et al., 2006).
5. Programming the neuroendocrine network that regulates appetite (Breier et al., 2001; López-Soldado et al., 2006; Ozanne & Hales, 2002).

2.1 Impairment of placental function

The placenta is the first of the foetal organs to develop and has several fascinating and critical functions by which it plays a direct part in foetal programming. Pre-pregnancy obesity is related to established hypertension and in some cases undiagnosed type 2 diabetes ("*Diabesity*") and it is associated with increased risk of placental dysfunction and foetal death as gestation advances. Epidemiological evidence has linked low birth weight and low placental weight to

foetal programming. So, foetal growth and the long-term determination of the future offspring are intimately linked to the regulation of the main functions of the placenta.

There is some evidence which suggest that a child of an obese or diabetic mother may suffer from exposure to a sub-optimal in uterus environment and that these early life adversities may extend into adulthood. Also, the development of gestational diabetes (GDM) is associated with a shift in the concentration of several hormones, cytokines, metabolites, and growth factors that may subsequently alter placental morphology and function with very serious consequences (Hiden & Desoye, 2010). One primary mechanism that linked maternal nutritional status and the predisposition of metabolic disease is related to altered placental functionalities (Farley et al., 2009). Maternal obesity in humans determines an increase of placental and adipose tissue macrophage infiltration, and also an increase of CD14+ expression in maternal peripheral blood mononuclear cells (PBMC) and maternal hyperleptinemia. It seems that chronic inflammation state of pre-gravid obesity is extending to in uterus life with accumulation of a heterogeneous macrophage population and pro-inflammatory mediators in the placenta (Challier et al., 2008). The resulting inflammatory milieu in which the foetus develops may have critical consequences for short and long term programming of obesity (Farley, 2009).

Foetal nutrient delivery depends on the complex interaction of maternal uterine and foetal umbilical blood flow, nutrient supply, placental microstructure and transport capacity.

The placenta is an important regulator of foetal growth, due to its roles in nutrient supply to the foetus, removal from the foetus of metabolic waste and hormone production (Higgins et al., 2011). The role of the trophoblast (both amount and function), in placental transporter activity, hormone production and substrate metabolism is being recently investigated. There is evidence that changes in the activity and expression of trophoblast nutrient and ion transporters are fundamental in determining foetal growth and the molecular mechanisms regulating trophoblast transporters, which are directly related to the development of pregnancy complications and foetal programming of cardiovascular and metabolic disease (Roberts et al., 2009). The concept of the placenta as a "*nutrient sensor*" has been reported by Jansson and Powell, 2007, introducing the idea about how the placenta coordinates nutrient transport functions with maternal nutrient availability. Thus the ability of the maternal supply line to deliver nutrients (i.e. placental blood flow, maternal nutrition, substrate and oxygen levels in maternal blood, etc.) regulates key placental nutrient transporters. With this perspective, placental transport alterations represent a mechanism to match foetal growth rate to a level which is compatible with the amount of nutrients that can be provided by the maternal supply line, making the placenta a *key player* in the regulation of foetal growth and, as a consequence, foetal programming.

2.2 Foetal adipose tissue formation

The period covering uterine implantation and rapid placental growth is a critical window of organogenesis. During this period there is a marked cell division within developing organelles preceding the structural development of many foetal tissues. Adipogenesis, which begins in uterus and accelerates in the neonatal period, is the leading candidate for the development of programming. In humans, after a short period of fat deposition during childhood, there is a rapid acceleration around 6 years, which will be relevant in case of a premature development of fatty tissue mass (before 5.5 years) in children, because it is associated with an increased adult obesity (Eriksson et al., 2002).

Currently there is evidence from studies both in humans and in sheep, that the synthesis and secretion of hormones produced by adipocytes such as leptin already have regulatory mechanisms in foetal life (Symonds et al., 2003). Small perturbations in the foetal adipose tissue growth and endocrine sensitivity may have important long-term effects (Symonds et al., 2004). The magnitude of these and subsequent changes in adipose tissue are determined by the maternal and foetal nutritional environment. The consequences depend on the stage where the change occurs, either in embryogenesis, the formation of the placenta or during foetal development. All three are critical windows and it has been shown that neural development and cardiovascular function are more sensitive to the influences during the embryonic period, whereas the renal system is more affected during placental development and adipose tissue is more affected in the stage of foetal development (Symonds et al., 2007). In humans, adipose tissue has its origin during the early stages of foetal life; during normal foetal development two adipocyte cell lines, white and brown (brown) will develop (Moulin et al., 2001). Foetal fat exhibits characteristics of both cell lines, showing an ontogenetic increase of the specific uncoupled protein (UCP-1) of brown adipose tissue (Clarke et al., 1997), along with a modest increase in leptin synthesis, produced primarily by white adipocytes. Foetal adipose tissue is formed by the combination of multilocular and unilocular cells (Yuen et al., 2003), of which the latter have few/ no mitochondria (Figure 2).

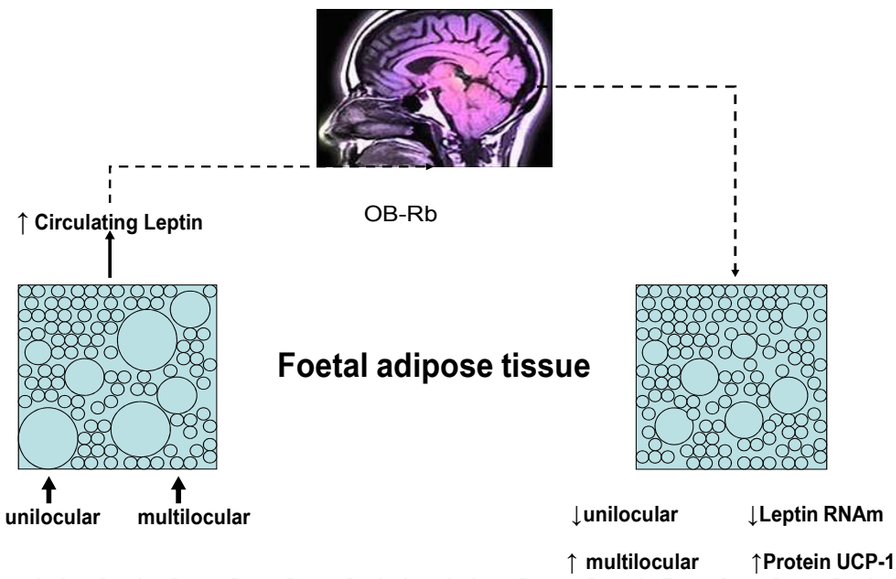

Fig. 2. Schematic diagram with a summary of the potential effects of increased circulating leptin concentrations on the structural and functional characteristics of foetal adipose tissue (modified from Yuen et al., 2003).

However, the proportional concentration increases after birth to have white adipose tissue as dominant. In lambs, after birth, there is an important endocrine stimulation that inhibits the synthesis of UCP-1 to undetectable levels at a month of life (Symonds et al., 2004). The decrease in UCP-1 is parallel to an increase in plasma leptin and the mRNA for the leptin synthesis for around the first week of life (Bispham et al., 2002) (Figure 3). The increased deposition in adipose tissue after the first week takes place independently of any change in leptin.

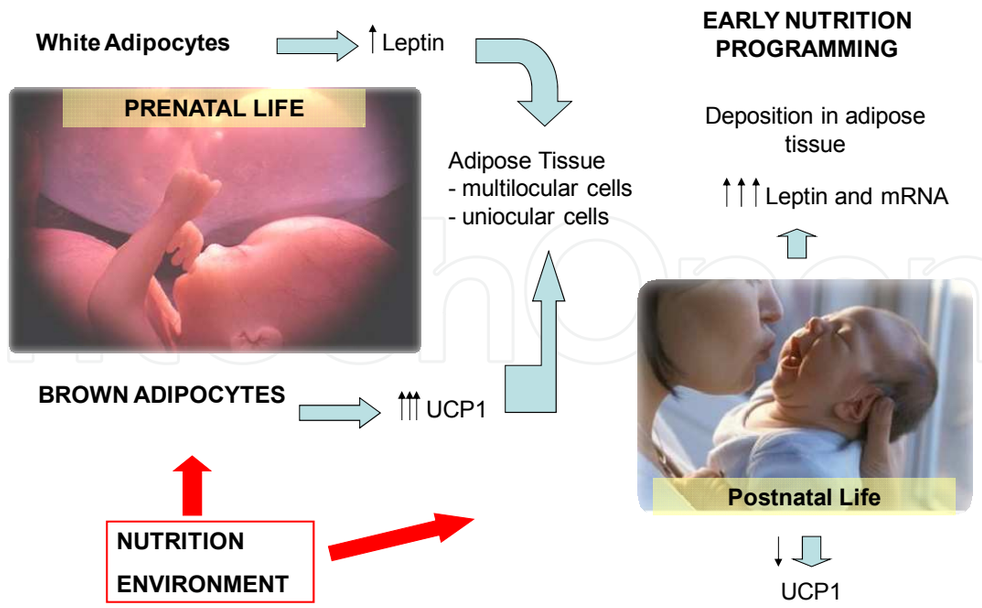

Fig. 3. Changes in the production of UCP1 and leptin during foetal and postnatal life.

It has been observed in sheep that a reduction in caloric intake of 50% during the period of implantation and placental development profoundly affects placental growth and morphology to a reduction of placental weight (Clarke et al., 1998). This takes place together with a low capacity for inactivation of maternal cortisol by the enzyme 11 hydroxysteroid dehydrogenase type 2 (11 β -HDS-2) (Whorwood et al., 2001), which occur in response to declining maternal plasma cortisol (Bispham et al., 2003). Gene expression in the placenta of both glucocorticoid receptors and uncoupled mitochondrial protein 2 (UCP-2) increases and this could partly contribute to the reduction that accompanies the decreased proliferation of placental cells after nutritional restriction (Gnanalingham et al., 2007). Birth weight, however, is not altered by this dietary manipulation and, although it has more fat, this adaptation does not persist into adulthood even though obesity is developed. It is unclear how the mother may influence foetal adipogenesis and determine the time of the "*fat rebound,*" but there is evidence of programming of the morphology and metabolism of the adipocyte. Like many other type of tissues, adipose tissue has the potential to grow limitlessly. But this diet-induced growth increases the number of fat cells in an apparently irreversible manner (Corbett et al., 1986). It should be expected a direct influence on the development of hyperplasia or fat hypertrophy in the baby after a maternal hipernutritive diet, because glucose is the major metabolic precursor of lipid synthesis; the direct infusion of glucose in the foetus is accompanied by a parallel increase in fat mass (Stevens et al., 1990), but the persistence of this effect into adulthood is not defined. Adipocyte hypertrophy also occurs in rats after weaning when the mothers were subject to pleasant diets during pregnancy and lactation (Bayol et al., 2005).

2.3 Genetic factors

Any molecular mechanism that justifies the programming of obese adult phenotype development must explain how early environmental stress can determine persistent molecular changes that give rise to profound damage that will affect health in adulthood.

2.3.1 Epigenetic programming of mitochondrial and nuclear genome

One of the molecular mechanisms by which maternal nutrition and metabolic status can influence foetal programming is the epigenetic alteration of foetal genome. These alterations may involve chromatin remodelling and regulation of gene expression. The characteristics of mitochondria in development are particularly suited to translate the early stress associated with development programming in the form of cellular dysfunction that can be observed in later periods of life. The levels of mitochondrial DNA (mtDNA) are exquisitely sensitive to environmental stress, and a suboptimal environment can produce a reduction in the quantity and quality of mtDNA by increasing the rate of mutations (Graziewicz et al., 2006; Taylor et al., 2005). Recent publications from human studies (Ruiz-Pesini et al., 2004; Wilson et al., 2004) and in experimental models of obesity and diabetes (Wisloff et al., 2005) imply that altered mitochondrial function at least contributes to the development of obesity and related conditions. MtDNA mutations are tolerated for many years before exceeding the threshold level of damage (Chinnery et al., 2002), which would explain the long-term influence of mitochondrial function with implications, in particular, on energy expenditure (Taylor et al., 2007; Wisloff et al., 2005).

2.3.2 Altered state of methylation

Persistent epigenetic changes in methylation status of nuclear DNA (nDNA) can deeply influence the programming of obesity (Blewitt et al., 2006; Lillycrop et al., 2005; Ollikainen et al., 2010; Waterland, 2006). In addition, the potential neurotrophic action of leptin can programme the genes involved in regulating centres of appetite and energy expenditure in the developing hypothalamus (Bouret et al., 2004). The alteration of methylation status in very early embryonic development may also contribute to the obese phenotype observed in embryo transfer and cloning processes. (Sakai et al., 2005). There is evidence that early nutrition has an effect on DNA methylation. Studies have shown that promoter DNA methylation of *PPARGC1A*, *PPARG*, and *Tfam* genes may be associated with newborns' anthropometric and laboratory variables, and with their mothers' pre-pregnant BMI. This suggests that maternal obesity may influence the offsprings' metabolism throughout several mechanisms, among them epigenetic regulation of many genes, such as *PPARGC1A* promoter methylation, and so the baby might be at risk of becoming obese in later life (Gemma et al., 2009). Early malnutrition (both under nutrition and overweight) with respect to methyl donors can cause what is known as "*epigenetic aging*", contributing to increased susceptibility to diseases present in adult life (Waterland & Jirtle, 2004). There is convincing data from animal models (Champagne et al., 2006; Lillycrop et al., 2008) and experimental data in human studies (Bjornsson et al., 2008; Christensen et al., 2009). The results of human studies strongly suggest an effect of prenatal exposure to adverse environments (such as exposure to famine or dietary supplementation) in determining the level of DNA methylation present in the offspring, specifically at imprinted genomic regions implicated in regulating foetal growth (Tobi et al., 2009). Rapid growth may lead to postnatal changes in programming the expression of some genes that had been predetermined in uterus. It has been shown that increased expression of insulin receptors is present in the offspring of rodents subjected to protein restriction (Martin-Gronert & Ozanne, 2005). The genetic susceptibility to insulin resistance or β cell dysfunction causes changes in foetal growth mediated by insulin, which results in a low birth weight and increased risk of developing type 2 diabetes in adulthood (Hattersley & Tooke, 1999). Insulin is a hormone promoter of foetal growth; insulin concentrations are positively related to glucose

levels in the foetus and birth weight. Since insulin acts both as a signal for normal energy balance and as antilipolytic agent, changes in the signs of insulin may have an effect on appetite and obesity. Three genes or DNA common loci have been identified and can be replicated as candidate genes regulators in the development of obesity: FTO, INSIG 2, MC4R (Hinney et al., 2007). Still, 4 of the most studied genes are involved in the development of foetal and postnatal adipose tissue, of which two are receptors, glucocorticoid receptor - GR, and the activated receptor for proliferation of peroxisome - PPAR (Robitaille et al., 2004), and two are metabolic enzymes, the 11 *β-dehydrogenase* type I hidroesteroide or 11 *β-HSD-1* (Itoh et al., 2004) and 11 *β-dehydrogenase* type II hidroesteroide - 11 *β-HSD-2* (Nuñez et al., 1999).
Persistent alteration in the expression of any of the many proteins that influence the development of adipocytes and lipolysis (i.e. *PPAR-γ*) can exert a permanent influence on adipocyte proliferation and cell hypertrophy processes. PPAR-γ proteins are the main regulators of adipocyte differentiation and have been considered important factors in controlling insulin sensitivity throughout the body. The PPAR-γ 1 and PPAR-γ 2 are generated from the same gene by alternative promoter usage and mRNA (Fajas et al., 1997). However, little is known about the regulation of PPAR-γ gene expression in human tissues (Rosado et al., 2006). The PPAR-γ are members of a nuclear receptor super family that heterodimerize with acid receptor 9-cis-retinoic acid (RXR) and is linked to specific response elements in promoter regions of target genes to change their rate of transcription (Kliewer et al., 2001). In humans, it can be differentiated in 28 amino terminals, but have the same binding domain. PPAR-γ 1 is preferentially expressed in adipocytes, but also in other cell types and tissues such as colon, epithelial cells of the gastrointestinal tract (Lefebvre et al., 1999), kidney, macrophages (Ricote et al., 1998) and, at a smaller extent, in skeletal muscle. In contrast, the expression of PPAR-γ 2 mRNA is largely restricted to adipocytes. PPAR-γ proteins are the main regulators of adipocyte differentiation (Lowell, 1999) and have been considered important factors in controlling insulin sensitivity throughout the body. The altered expression of adipocyte proteins has been demonstrated in mothers suffering from malnutrition {(adipocytes of lambs subject to a restrictive diet in prenatal life show an increase in the expression of 11 *β-HSD-1* and GR}, which leads to increased exposure to cortisol and increased proliferation of adipocytes (Reynolds et al., 2001; Gnanalingham et al., 2005). Human studies have shown that the expression of 11 *β-HSD-1* in subcutaneous fat is correlated with BMI, suggesting a potential therapeutic role of selective antagonists in humans (Wake &Walker, 2004). The programming of PPAR-γ has been demonstrated in the liver of children exposed to a diet deficient in protein during foetal life and has been linked to an altered state of methylation (Lillycrop et al., 2005). These are potentially important molecular targets in programming the development of obesity and have yet to be explored in depth.

2.3.3 Mutation in the leptin gene.

Leptin is an adipocyte-derived hormone that suppresses food intake and increases energy expenditure by binding to and activating its specific receptor in the hypothalamus. Monogenic mutations in the leptin gene (LEP) and the leptin receptor gene (LEPR) have been shown to cause morbid obesity in mice (Oswal & Yeo, 2007) and humans (Beckers et al., 2009). The leptin gene is positioned in the chromosome 7q22-35 and is the most prominent candidate gene linked to body mass index (BMI). The leptin receptor, also identified as the diabetes gene product, is a single transmembrane protein that is established in many tissues and has several alternatively spliced isoforms.

There is little epidemiological evidence for an association between circulating leptin and obesity. It has been shown that small-for-gestational age and preterms have lowered leptin levels. Family history of obesity has been correlated with high umbilical cord levels of leptin (Hanley et al., 2010). Several studies investigated the impact of single nucleotide polymorphisms (SNPs) in the LEP or LEPR genes on adiposity markers, but the results are not conclusive (Paracchini et al., 2005). In addition, the association between these SNPs and body size at birth has been little studied (Souren et al., 2008), and whether body size at birth interacts with LEP and LEPR polymorphisms and later adiposity is unknown. There are however some SNPs of LEP gene involved in obesity physiopathology, such as A19G, A2548G in LEP gene, and Q223R in LEPR gene. It seems that mutations in the leptin gene lead to defective leptin production and cause recessively inherited early onset obesity (Mammes et al., 1998). Obese individuals homozygous for the G-allele showed significantly lower leptin concentration compared to obese patients either heterozygous or homozygous for the A-allele after correction for BMI (Jiang et al., 2004). Recently, it has been shown that LEP -2548GG genotype appears to be important in regulating leptin levels, whereas the LEPR 223R allele might predispose healthy subjects to develop metabolic disturbances (Constantin et al., 2010). Mutations of the promoter or the regulatory sites could affect the expression of LEP and explain the linkage of obesity with the microsatellite markers (Mammes et al., 1998). The frequencies of the LEP G/G homozygote (with Mendelian recessive and codominant models) were showed to be higher in the extremely obese subjects (BMI >35 kg/m^2) (Wang et al. 2006). The common G allele of G-2548A is overtransmitted in the obese offspring (Jiang et al. 2004b). G-2548A was associated with a difference in BMI reduction following a low calorie diet in overweight women (Mammes et al., 1998). The G−2548A substitution either is located in a regulating site specific for LEP and a mutation created probably correlates with regulating of the promoter regions. It must be confirmed that genetic variations at the *LEP* locus induce changes in leptin levels or metabolism, and that these changes are associated with differences in the predisposition to obesity or in the response to a low-calorie diet. None of these variants were associated with BMI in subjects on spontaneous diet (Mammes et al., 1998). The protein encoded by LEPR gene belongs to the gp130 family of cytokine receptors that are known to stimulate gene transcription via activation of cytosolic STAT proteins. This protein is a receptor for leptin and is involved in the regulation of fat metabolism, as well as in a novel hematopoietic pathway that is required for normal lymphopoiesis. Mutations in this gene have been associated with obesity and pituitary dysfunction. Alternatively spliced transcript variants encoding different isoforms have been described for this gene. In the 223 codon in mRNA sequences the mutation CAG→CGC was detected, that corresponds to Gln→Arg change in peptide molecule. In humans, Gln223Arg polymorphisms of LEPR have been associated with higher blood pressure levels, hyperinsulinaemia, glucose intolerance and higher BMI. Gln223Arg polymorphism is within the region encoding the extracellular domain of the leptin receptor and may change functional characteristics of this molecule This mutation results in abnormal splicing of leptin-receptor transcripts and generates a mutant leptin receptor that lacks both transmembrane and intracellular domains. The mutant receptor circulates at high concentrations, binding leptin and resulting in very elevated serum leptin levels (Lahlou et al., 2000). The association of the LEPR p.Q223R polymorphism with obesity was related to the co-dominant and dominant model, but not with the recessive model. There is the hypothesis that the p.Q223R LEPR variant is associated with a BMI increase. It has been proposed the hypothesis that variation of LEPR is participating in the union with leptin and influence on leptin serum levels. Therefore, leptin levels can influence on iron metabolism.

2.4 Impact of prenatal nutrition and birth weight on programming and the development of obesity

Changes in nutritional intake for both mother and foetus may have a profound effect on a range of metabolically important tissues. These mechanisms have the potential to protect the newborn against the adverse effects on the development of later obesity and its accompanying complications (Sébert et al., 2008). There is a potential impact of the prenatal nutritional experience on the development of endocrine and neuroendocrine systems that regulate energy balance, with particular emphasis on the role of hormones produced by adipocytes, especially leptin. In rodents, maternal leptin exerts a strong influence on the development of the appetite-regulating neural network and the consequent regulation of leptin synthesis and the risk of obesity in children. Recently, there is evidence, both in humans as in lambs, that the synthesis and secretion of the hormones produced by adipocytes like leptin already have regulatory mechanisms in foetal life (Symonds et al., 2003). Furthermore, hypothalamic neuropeptides that regulate food intake and energy expenditure in adulthood, are also present in the foetal brain and may regulate, through maternal reference levels, the foetal nutrient uptake and hormonal signals, including leptin. These results are important to determine what mechanisms are developed in the "*fat tissue-brain axis*' at the beginning of life, which will precede the development of adult obesity (McMillen et al., 2006).

The effect of maternal diet on the basal metabolism of children is still largely unknown and it has only been studied superficially in models of malnutrition. Yura et al., 2005, have demonstrated conclusively the dietary induction of thermogenesis in adult mice born from mothers with nutritional restriction during gestation (Yura et al., 2005), verifying a reduction in oxygen consumption and carbon dioxide production compared with control animals when a diet high in fat is maintained. The administration of leptin during pregnancy and lactation in pregnant rats subjected to protein restriction determines offspring with increased metabolic rate resistant to obesogenic diets (Stocker et al., 2004). It has also been shown in lambs that protein restriction during pregnancy program abnormal thyroid function in the offspring, which influences basal metabolic rate (Rae et al., 2002). In addition, this animal model has also shown that changes occur in fat mass and mitochondrial function in foetal adipose tissue, associated with an alteration of thermogenesis (Symonds et al., 2004). Polyunsaturated fatty acids of the n-3 series, especially docosahexaenoic acid (C22: 6 n-3, DHA), play an important role in the prevention of certain diseases including type 2 diabetes, insulin resistance, hypertension, cardiovascular disease, and so on. (Simopoulos, 1999). The n-3 fatty acids ingested in diet can alter the composition of the phospholipids of the cell membrane, determining the synthesis of eicosanoids and regulate their activity. Recent studies suggest that these fatty acids are important mediators of gene expression through activation of PPARs by controlling the expression of genes involved in lipid metabolism, glucose and adipogenesis (Jump, 2002; Lombardo et al., 2006). The increase of palmitic acid and saturated fatty acids in plasma triglycerides in newborns of diabetic mothers, along with the decrease in polyunsaturated fatty acids n-3 series and n-6, suggest metabolic pathways in this population may program obesity.

It has been seen in studies with pigs that birth weight has important implications on the development of skeletal muscle and adipose tissue (Mostyn et al., 2005). An important regulator of the metabolism of these tissues is the transport of fatty acids from the plasma membrane to intracellular organelles. This process of fatty acid utilization is carried out by the family of fatty acid binding proteins (FABP) that regulate the range of cellular processes. It has

been observed a profound alteration of gene expression of FABP4 and FABP3 in adipose tissue and skeletal muscle between normal newborns and small and large for gestational age, indicating impaired fatty acid utilization. These adaptations are related to differences in the size of adipocytes and could be indicators of the degree of metabolic disease appearing in adult life due to differences in deposition and fat metabolism in infants that are not in the normal weight percentiles for gestational age (Sébert et al., 2008). Moreover, few studies have investigated the activity of newborns prenatally exposed to maternal obesity or a state of over nutrition; however malnutrition during gestation followed by a nutritionally rich postnatal state, determines the children's programming appetite showing hyperphagia and reduced locomotor activity, associated with obesity (Vickers et al., 2000, 2003). An animal model where mice were fed a diet rich in polyunsaturated fatty acids through gestation determined an increase in motor activity in the offspring (Raygada et al., 1998). In another animal model in which mothers were fed a diet saturated in fats, it was observed the programming of reduced locomotor activity (Khan et al., 2003). These studies suggest that the fatty acid composition of maternal diet is crucial in programming activity levels and therefore energy expenditure.

2.4.1 Birth weight and obesity in adults

The relationship between birth weight and adiposity, measured in childhood and adulthood, is generally positive, although some studies have shown a parabolic relationship with J or U shape between birth weight and adult fat mass, with high prevalence of obesity that would occur in individuals with low or high birth weight (Parsons et al., 2001). A determinant factor for health and longevity is the index "placenta / foetal size". Foetuses with a placenta disproportionately large or small have increased standardized mortality rates. In newborns it has been demonstrated the presence of a positive correlation between plasma leptin concentrations in cord blood and birth weight or neonatal adiposity. In pregnancies complicated by maternal diabetes, the foetus is hyperglycemic and hyperinsulinemic and hiperleptinémic (Cetin et al., 2004). Alterations in the programming of leptin synthesis, its secretion or its mechanisms of action, may be decisive in the early origins of obesity on nutritional exposure after both above and below the requirements in the foetal or neonatal early life. It has been suggested that the influence of maternal weight on the relationship between birth weight and increased BMI may operate through the impact of high maternal nutrient intake and high foetal uptake.

The hypothesis of teratogenesis mediated by the passage of energy substrates to the foetus (Freinkel, 1980), suggests that in women with gestational diabetes, uterine foetal exposure to excess energy nutrients such as glucose will determine a permanent change in foetal metabolism, causing malformations, increased birth weight (macrosomy or neonatal obesity), and an increased risk of developing type 2 diabetes in adulthood (Boney, 2005; Silverman et al., 1995). However, despite considering the theory of excess maternal nutritional intake as a cause of foetal macrosomy in children of diabetic mothers, the current diagnostic criteria for gestational diabetes may not be sufficient to differentiate between diabetogenic and non-diabetogenic pregnancies (Simmons et al., 2002). In the case of *obese mothers with glucose intolerance,* especially in *diabetics,* the maternal and foetal plasma levels of glucose are higher, causing higher birth weight in children and higher BMI in adulthood with a high risk of developing obesity and glucose intolerance (King, 2006; McMillen et al. 2006) (Figure 4). Therefore, the genetic base and the intrauterine/neonatal nutritional environment will condition a hormonal response that can lead to the development of morbidity from overweight.

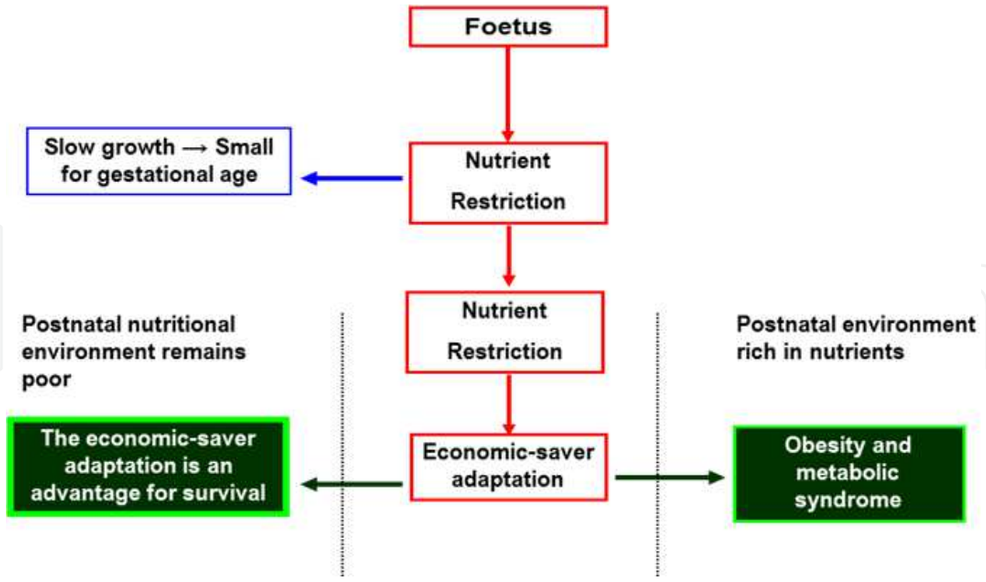

Fig. 4. Potential mechanisms explaining the relationship between high birth weight and adult obesity (Modified from McMillen, 2006).

The manipulation of both metabolic and hormonal environment in the mother as a result of decreased dietary intake at the end of pregnancy may act by determining the reduction of adipose tissue deposition in the foetus. Exposure to a reduced supply of nutrients during the first trimester of pregnancy, as occurred in the Dutch Winter Famine in 1944-1945, also determines an increase in fat mass in adulthood (Ravelli et al., 1976). Infants born small for gestational age (SGA) also show a marked reduction in body fat mass at birth, which mainly reflects the decrease in lipid accumulation in adipocytes (Levy-Marchal et al., 2004). While plasma leptin concentrations are low at birth in infants with intrauterine growth retardation, it increases to a high level compared with infants with normal birth weight (Jaquet et al., 1999). Children with low birth weight and malnourished at birth, and subsequently experience a period of very rapid growth during the first months of life, are more vulnerable to developing obesity, insulin resistance and cardiovascular disease (Eriksson et al., 2002) (Figure 5). Newborns with low birth weight for gestational age tend to have a lower BMI in adulthood than those who were large at birth; furthermore, the latter show a more central distribution of obesity, a significantly reduced muscle mass and a high body fat in adolescence and adulthood (Loos et al., 2001, 2002).

It is now known that infants with low birth weight are candidates for the development of obesity from age five. This fact directly related to a relative oversupply of nutrients in the neonatal period "*economic-saver phenotype*" of Barker (Gluckman et al., 2004; Hales & Barker et al., 2001). As a result, small perturbations in the foetal adipose tissue growth and endocrine sensitivity can have important long-term consequences. When in uterus, the foetus has been subjected to nutritional restriction and postnatal exposed to an obesogenic environment the baby will show an amplified insulin response that is not accompanied by other physiological or metabolic adverse responses for the development of obesity; It has even been observed that the kidneys seem to be protected against the adverse effects after induced obesity like glomerulosclerosis (Williams et al., 2007). One of the factors that seem to be important in renal protection is the magnitude of cellular adaptation to the cell stress of the perivisceral fat, which

is upregulated in newborns of mothers who had nutritional restriction during gestation. However, during adolescence, fat mass increases and these children are insulin resistant even though basal insulin is not impaired (Mostyn et al., 2005). Potentially adverse effects do not seem to be amplified after exposure to an obesogenic environment.

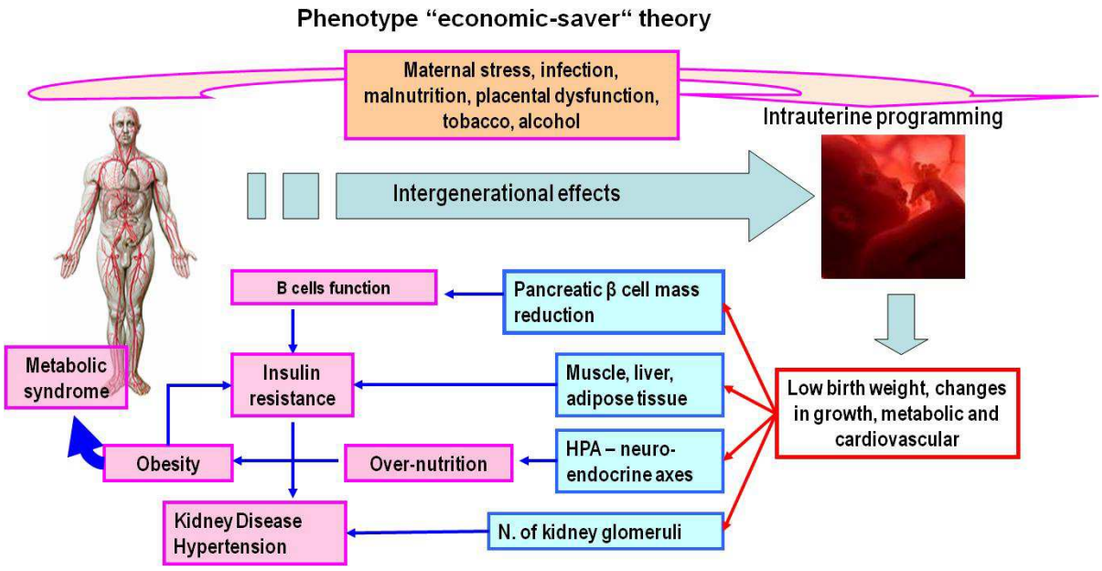

Fig. 5. Potential mechanisms explaining the relationship between low birth weight and obesity and metabolic syndrome in adults (Modified from McMillen, 2006).

The growth rate during early postnatal life may also influence the long-term health of an individual. The increase of the growth rate in the early postnatal period, also called "*catch-up growth*" is present in 30% of all children in any population well fed and occurs primarily in those who were underweight and had low length at birth. It has been suggested that the "*catch-up*" that occurs in the first 2 years is a mechanism that aims to restore the size that the child was supposed to have genetically. However, even though it presents short-term benefits, this situation is not positive in the long term because these children are going to exceed their genetic established target and will develop elevated body mass index and fat accumulation in the trunk. Levels of IGF-1 at 5 years of age are directly related to weight gain between 0 and 2 years (McMillen et al., 2006). Sayer, et al. have shown that infants suffering from intrauterine growth retardation and low birth weight develop alterations of body composition in adult life (Sayer et al., 2004). There is scientific evidence that nutrition in early postnatal life plays a role in the ability of leptin synthesis by adipocytes. It has been observed that the leptin / fat mass indices in teenagers is significantly higher in those who received enriched formula in comparison with those who received standard formula or human milk (from milk Banks) after a preterm birth. (Singhal et al., 2002). The protective effect of maternal milk on the development of obesity has also been widely tested (Koletzko et al., 2005; Li et al., 2003).

2.5 Programming of appetite

The action of the hypothalamus in controlling food intake is widely recognized, but only recently it has been shown to be an essential part in development programming associated with neonatal exposure to high-caloric diets (Cripps et al., 2005; McMillen et al., 2005;

Plagemann, 2005, 2006). In rodents, the hypothalamic nucleus continues to differentiate until day 20 of postnatal life (Grove et al., 2005); this period is therefore critical for studying the expression of key regulatory neuropeptides and receptors in the hypothalamus, the expression of which is permanently programmed through maternal-foetal dietary factors. The investigation of postnatal neuronal development in these animal models is directly relevant and applicable to other species, even for humans, since the extent of neuronal development also occurs in breast-feeding with hypothalamic maturation that begins at the uterus and continues in early postnatal life.

2.5.1 Central regulation of appetite

Neural circuits that mediate homeostatic functions such as eating patterns are distributed by various brain structures. Within these there are specific regions of the hypothalamus like the arcuate nucleus (ARC), ventromedial nucleus (VMN) and the lateral area. The solitary tract nucleus (STN) is also involved in food regulation. Neurons in this nucleus receive signals from vagus nerve with satiation stimulus. STN neurons have reciprocal connections with the forebrain areas such as the paraventricular nucleus (PVN) and the substrates have to respond to hormonal central effector peptides involved in energy homeostasis {(MC4 receptors, leptin receptors, and neurons containing propiomelanocortin (POMC)}. The hypothalamus is part of a system which integrates the regulation of body composition with food intake and energy expenditure. A series of stimuli in different systems related to the metabolic state are received in the hypothalamus, which modulate the release of hypothalamic peptides that regulate food intake and hypothalamic pituitary axis. The main hypothalamic areas involved in the regulation of eating behaviour are: 1) The VMN, where a possible lesion produces voracity and obesity. 2) The lateral hypothalamic area (LHA), whose injury produces decreased nutritional intake and anorexia. 3) The PVN, which receives information from other brain nuclei related to intake. 4) The ARC, whose neurons produce peptides that regulate food intake, stimulating it - as the neuropeptide Y, - or inhibiting such as POMC / *transcript regulated by cocaine and amphetamine* (CART). The two circuits send their signals primarily to PVN and also to other hypothalamic nuclei which directly modulate eating behaviour. Both circuits are influenced by peripheral hormones that can cross the hematoencephalic barrier. These cores are interconnected and the circuits generated in this brain area have a specialized role in energy homeostasis. The hypothalamus also receives different stimuli from the central nervous system (vagal and catecholaminergic), hormonal stimuli (insulin, leptin, cholecystokinin, and glucocorticoids) and gastrointestinal hormonal stimuli (ghrelin, peptide YY) (Schwartz & Brain, 2001).

The ARC is a critical component in the regulation of body weight located adjacent to the base of the 3rd ventricle in the mediobasal hypothalamus. Contains neurons that have axon terminals in direct contact with blood flow, although protected by the blood-brain barrier; these neurons are known as "the first-order neurons." They are able to sense and respond to hormonal ranges and nutrient signals such as insulin, leptin, ghrelin and glucose (Schwartz & Brain, 2001). There are 2 distinct groups of neurons in the ARC that will regulate energy balance. A group of them co-express neuropeptide Y (NPY) and related peptide agouti (AgRP), and another group of neurons co-expressing the POMC and CART (McMillen et al., 2005). The ARC is projected onto other second-order neurons, and these in turn project to other neurons of the solitary tract nucleus. Afferents related to satiety are transmitted to the STN in turn connected to ARC, via the vagus nerve and sympathetic fibres from the liver

and the gastrointestinal tract by peptides such as cholecystokinin (CCK). The connections between the ARC and other key sites in the central nervous system are known to regulate the dietary intake and energy balance in early postnatal life. Innervations between the ARC and PVN are present in the human foetus at 21 weeks gestation, although the density of these projections is greatly increased in the postnatal period (Grove et al., 2003).

Appetite and energy balance are regulated primarily by hypothalamic neuropeptides expressed in the adult. Neurons co-expressing NPY / AgRP are part of the energy balance anabolic pathway. Both NPY and AgRP are inhibited by leptin and insulin. The increase in NPY signals as a result of a decrease in energy balance not only determines hyperphagia and weight gain, but also contributes to systemic insulin resistance and glucose intolerance. By contrast, AgRP exerts an anabolic effect through antagonism of neuronal melanocortin receptors (MC3-R and MC4-R) that are involved in regulating appetite. Prolonged inhibition of melanocortin receptors determines weight gain and insulin resistance. The MC4-R mutations in humans are associated with obesity phenotypes (McMillen et al., 2005). In overfed newborn rats it has been observed an increase in adiposity (Davidowa & Plagemann, 2004). It has been shown that the overfeeding of rats with small amounts in the neonatal period, determines the development of hyperphagia, fat deposition and accelerates weight gain associated with hyperleptinemia and central leptin-resistance at the level of the arcuate nucleus (Velkoska et al., 2005). These studies suggest a bad programming of the hypothalamus that would take place during lactation. Kozak et al. (2000) have shown a direct involvement of the hypothalamus in the programming of obesity, having observed that adult offspring of rats fed a diet rich in fat (55% margarine) show an exaggerated response to food after injection of Neuropeptide Y (NPY) in the lateral ventricle, eating twice more than control animals (Kozak et al., 2000). Prenatal over nutrition in sheep also led to a change in appetite regulation in the early postnatal period (Muhlhausler et al., 2006).

2.5.2 Leptin

It has been suggested that high concentrations of circulating leptin determine a misalignment of the action of leptin and its receptors in the hypothalamus, thus there would be a disruption on the route of signal transduction that is required for suppression of appetite (Ahima & Flier, 2000). Leptin is synthesized in adipose tissue, with the size of adipocytes the determinant factor of this synthesis. Adipose tissue secretes the protein ob (leptin) that circulate in the blood reaches the ventromedial nucleus of the hypothalamus where it binds to its receptor, encoded by the gene db. This results in a decrease of NPY from the ARC, which suppresses appetite and increases the levels of norepinephrine from sympathetic terminals that innerve adipose tissue and affect other hormone actions, such as insulin secretion (Figure 6).

Sex is also important; there are higher levels of leptin in women compared to men, for an equivalent in mass (Martin-Gronert & Ozanne, 2005). The leptin receptor (ObRb) activates the Janus kinase (JAK), which phosphorylates some members of the pathway of signal transduction and transcription (STAT). Activation of the leptin receptor also induces the expression of suppressor of cytokine signalling--3 (SOCS-3), which in turn inhibits the subsequent signal transduction of leptin. The SOCS-3 can also potentially inhibit signals from Ins-Rb. In addition, sensitivity to insulin and leptin increases in the SOCS-3 of rats, giving them protection against the development of diet-induced obesity. Moreover, SOCS-3 is a key candidate for the regulator of diet-induced leptin as well as in the case of insulin

resistance. The presence of functional leptin receptors in pancreatic β cells and the observation that leptin directly inhibits insulin secretion, leads to the concept of "axis adipoinsular" (Kieffer & Habener, 2000) by which insulin stimulates adipogenesis and synthesis of leptin and leptin inhibits the production of insulin in the pancreas. It is proposed that the pancreatic resistance to leptin may be a mechanism that promotes obesity often associated with hyperinsulinemia and may contribute to later development of diabetes in obese individuals (Seufert et al., 1999).

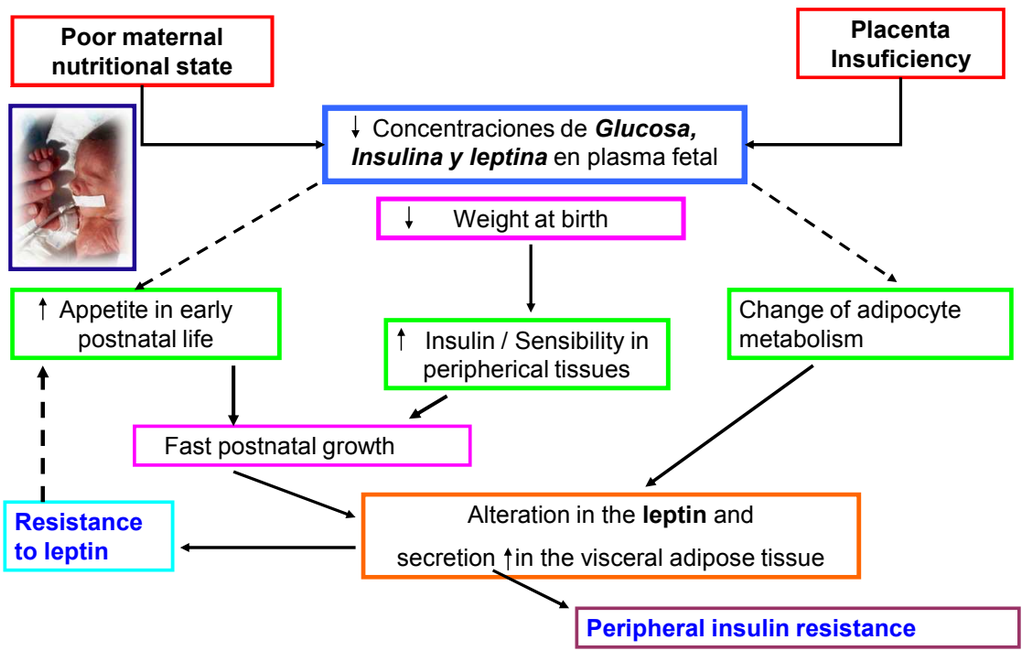

Fig. 6. Adipose tissue secretes the protein ob (leptin) that reaches the blood circulating through the hypothalamic ventromedial nucleus where it binds to its receptor, encoded by the gene db.

It has been shown a pivotal role of leptin in the programming of hypothalamic obesity after a study where leptin administered subcutaneously in the postnatal period (3-13 days) reversed the hyperphagia and obesity in adult rats born of rats with low dietary intake (malnutrition) (Vickers et al., 2005). A similar effect has been demonstrated by Yura et al. in normal rats observing that the early injection of leptin (8-10 days postnatal) determines an obese phenotype in the adult rat (Yura et al., 2005). A study in the developing hypothalamus in rats has shown that leptin promotes neuronal growth from the ARC to the paraventricular nucleus (PVN) during lactation, promoting a very close connection in neuronal hypothalamic regulatory system of appetite. Leptin appears to take part in the differentiation of 2 opposing pathways that control energy intake, promoting the development of the appetite stimulant NPY and agouti-related peptide projection (AgRP) from the ARC to the PVN by neural connections from melanocyte stimulating hormone-(α-MSH) - appetite suppressant derived from the POMC and present in all neurons (Bouret & Simerly, 2006; Horvath & Bruning, 2006).

Some programming models have shown evidence of impaired control of the sympathetic system (Khan et al., 2003), and a specific programming in neonatal hypothalamus by hyperleptinemia may also contribute to increased sympathetic tone that is intended for the development of hypertension-related obesity. In established obesity, there is a high level of circulating leptin, a selective resistance to leptin at the hypothalamic level that determines in part the attenuation of the anorectic leptin actions and of weight loss, and on the other hand, the preservation of vase-pressure actions of leptin at the central level that contribute to elevated blood pressure (Haynes, 2005). The selective leptin resistance causes a reduced availability of leptin to activate signalling mechanisms in the areas of appetite regulation of the ARC, keeping the sympathetic excitatory action of leptin in the cardiovascular system, related to the ventromedial nucleus (VMN) and dorsomedial (DMN) of the hypothalamus (Marsh et al., 2003). Given the neurotrophic role of leptin during the neonatal hypothalamic plasticity period, it seems that maternal hyperleptinemia and / or neonatal in the immediate postnatal period could program the selective resistance to leptin and thus the propensity for obesity and obesity-related hypertension (Howard et al., 2004).

2.5.3 Insulin: Glucose control and peripheral regulator of appetite

Insulin is secreted by pancreatic β cells in response to increased circulating glucose, amino acids or glucagon, as well as after stimulation of sympathetic nerve pathways (α) and parasympathetic (cholinergic). In adults, the β-cell mass is controlled by at least four independent mechanisms: a) β cell replication, b) β cell hypertrophy c) β cell neogenesis, d) β-cell apoptosis. The rate and type of response used depends on the adaptation of β cell mass to metabolic changes throughout adult life (Bonner-Weir, 2000). Insulin is the primary circulation factor involved in the control of body weight by the central nervous system (CNS). Insulin circulates in plasma at levels proportionate to the size of energy stores and enters the CNS in proportion to the plasma concentrations by a carrier linked to a specific receptor. Exogenous insulin administered directly into the brain, determines the reduction of food intake and body weight. The action of insulin in the brain is necessary for the upkeep of glucose homeostasis. The insulin receptor (Ins-Rb) is expressed in the ARC and the VMN and in the striatum and in the choroid plexus. Prolonged or chronic actions of insulin signalling will result in hyperphagia, increased plasma insulin and decreased sensitivity to insulin (Taylor & Poston, 2007).

3. Conclusions, public health messages and possible interventions

Recently, it has been reported that obesity during pregnancy clearly increases the risk of successful pregnancy after the study of 150000 Swedish women (Villamor et al., 2006), but also endangers the health of children, and in terms of public health, the health of future generations. The long term ultimate goal should be to reduce the incidence of obesity during pregnancy and increase public awareness of the importance of a balanced diet before and during pregnancy. The Obesity Committee of the American College of Obstetricians and Gynaecologists, have suggested that obstetricians should give pre-conception counselling and education about potential complications and should strongly recommend to obese patients to participate in a weight reduction program before pregnancy (American College of Obstetricians and Gynecologists [ACOG], 2005). So far, no similar recommendations have been made in Europe.

Recent research suggests that it should be avoided weight gain between pregnancies, and women should try to reach the initial weight before pregnancy before becoming pregnant again (Villamor et al., 2006). The Public Affairs Committee of the Teratology Society has also recommended counselling women about appropriate caloric intake, exercise and education about infant nutrition and the importance of breastfeeding (Scialli, 2006). However, although the benefits of breast-feeding are widely recognized, long term breastfeeding may promote obesity (Harder, 2005), and also, the milk of diabetic mothers and obese may be obesogenic to the developing baby (Rodekamp et al., 2005). To avoid rapid growth during the first year of life, infant formulas must be optimized. From a nutritional perspective, future research should focus on the identification of maternal nutritional insults that can be vectors of "health programming in your child," for example, the role of fat vs. carbohydrates and the saturated fat vs. unsaturated fats. Medically, the most effective treatment of maternal obesity and gestational diabetes, and specifically the control of hyperglycemia, hyperinsulinemia and hyperleptinemia, both before and during pregnancy can help to prevent programming of obesity.

In the future it is envisaged the use of pharmacological interventions with drugs that inhibit food intake but also peripheral acting drugs that modify the metabolism and energy balance as the antagonists of the 11β-HSD-1 (Wang et al., 2006). Agonists of PPAR-α and PPAR-γ, including the glitazones may improve insulin resistance (Guo & Tabrizchi, 2006) and enhance mitochondrial biogenesis in adipose tissue (Bogacka et al., 2005), offering a dual PPAR agonist therapy to treat risk factors of obesity (Gervois et al., 2004). There are also potentially effective new drugs acting on the cascade of signals related to adipocyte differentiation (Rodriguez et al., 2006). However, until the safety and efficacy of these drugs are proven, interventions on diet and lifestyle are the only resources available to fight obesity, especially during pregnancy. As for possible interventions in children, early identification of children at risk by measuring the rate of growth / BMI and early assessment of adiposity during the first years of life, and the identification of potential biomarkers of future obesity, could help to advise treatment with an early improvement of lifestyle and drug therapy in those at high risk. Research in this field offers a real chance to achieve strategies that can enable the effective prevention of obesity in future generations.

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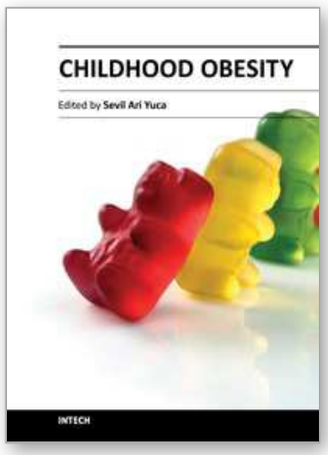

Childhood Obesity

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This book aims to provide readers with a general as well as an advanced overview of the key trends in childhood obesity. Obesity is an illness that occurs due to a combination of genetic, environmental, psychosocial, metabolic and hormonal factors. The prevalence of obesity has shown a great rise both in adults and children in the last 30 years. It is known that one third of children who are obese in childhood and 80% of adolescents who are obese in their adolescent years continue to be obese later in life. Obesity is an important risk factor in serious illnesses such as heart disease, hyperlipidemia, hyperinsulinemia, hypertension and early atherosclerosis.

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